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Characteristics of Growth in Children With Classic Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency During Adrenarche and Beyond

Troger, Tobias ; Sommer, Grit ; Lang-Muritano, Mariarosaria ; Konrad, Daniel ; Kuhlmann, Beatrice ; Zumsteg, Urs ; Flück, Christa E

Abstract: Context: Patients with classic congenital adrenal hyperplasia (CAH) often fail to achieve their full growth potential. Adrenarche may accelerate bone maturation and thereby result in decreased growth in CAH. Objective: To analyze the impact of growth during adrenarche on final height of adequately treated classic CAH patients. Design: Retrospective, multi-center study. Setting: Four academic pediatric endocrinology centers. Participants: Forty-one patients with classical CAH, born between 1990 and 2012. Main outcome measures: We assessed skeletal maturation (bone age), growth velocity and (projected) adult height outcomes, and analyzed potential influencing factors, such as sex, genotype, and glucocorticoid therapy. Results: Patients with classic CAH were shorter than peers ($-0.4\text{SDS} \pm 0.8\text{SD}$) and their parents (corrected final height $-0.6\text{SDS} \pm 1.0\text{SD}$). Analysis of growth during adrenarche revealed two different growth patterns: patients with accelerating bone age (49%), and patients with non-accelerating bone age compared to chronological age (BA-CA). Patients with accelerating BA-CA were taller than the normal population during adrenarche years ($p=0.001$) and were predicted to achieve a lower adult height SDS (-0.9SDS , 95%CI $-1.3;-0.5$) than non-accelerating patients when assessed during adrenarche (0.2SDS , 95%CI $-0.3;0.8$). Final adult height was similarly reduced in both accelerating and non-accelerating BA-CA groups (-0.4SDS , 95%CI $-0.9;0.1$ vs -0.3SDS , 95%CI $-0.8;0.1$). Conclusions: Patients with and without significant bone age advancement, and thus differing height prediction during adrenarche, showed similar (predicted) final height when reassessed during pubertal years. Bone age alone should not be used during adrenarche as clinical marker for metabolic control in CAH treatment. Keywords: adrenarche; classic CAH; final height prediction; growth.

DOI: <https://doi.org/10.1210/clinem/dgab701>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-209797>

Journal Article

Published Version



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Originally published at:

Troger, Tobias; Sommer, Grit; Lang-Muritano, Mariarosaria; Konrad, Daniel; Kuhlmann, Beatrice; Zumsteg, Urs; Flück, Christa E (2022). Characteristics of Growth in Children With Classic Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency During Adrenarche and Beyond. *Journal of Clinical Endocrinology Metabolism*, 107(2):e487-e499.
DOI: <https://doi.org/10.1210/clinem/dgab701>

Clinical Research Article

Characteristics of Growth in Children With Classic Congenital Adrenal Hyperplasia due to 21-Hydroxylase Deficiency During Adrenarche and Beyond

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Abbreviations: 17-OHP, 17-hydroxyprogesterone; BMI, body mass index; CAH, congenital adrenal hyperplasia; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulfate; SDS, standard deviation score; zR, zona reticularis.

Received: 1 August 2021; Editorial Decision: 17 September 2021; First Published Online: 2 October 2021; Corrected and Typeset: 12 October 2021.

Abstract

Context: Patients with classic congenital adrenal hyperplasia (CAH) often do not achieve their full growth potential. Adrenarche may accelerate bone maturation and thereby result in decreased growth in CAH.

Objective: The study aimed to analyze the impact of growth during adrenarche on final height of adequately treated classic CAH patients.

Methods: This retrospective, multicenter study (4 academic pediatric endocrinology centers) included 41 patients with classical CAH, born 1990–2012. We assessed skeletal maturation (bone age), growth velocity, and (projected) adult height outcomes, and analyzed potential influencing factors, such as sex, genotype, and glucocorticoid therapy.

Results: Patients with classic CAH were shorter than peers (-0.4 SDS \pm 0.8 SD) and their parents (corrected final height -0.6 SDS \pm 1.0 SD). Analysis of growth during adrenarche revealed 2 different growth patterns: patients with accelerating bone age (49%), and patients with nonaccelerating bone age relative to chronological age (BA-CA). Patients

with accelerating BA-CA were taller than the normal population during adrenarche years ($P = 0.001$) and were predicted to achieve lower adult height SDS (-0.9 SDS [95% CI, -1.3 ; -0.5]) than nonaccelerating patients when assessed during adrenarche (0.2 SDS [95% CI, -0.3 ; 0.8]). Final adult height was similarly reduced in both accelerating and nonaccelerating BA-CA groups (-0.4 SDS [95% CI, -0.9 ; 0.1] vs -0.3 SDS [95% CI, -0.8 ; 0.1]).

Conclusion: Patients with and without significant bone age advancement, and thus differing height prediction during adrenarche, showed similar (predicted) final height when reassessed during pubertal years. Bone age alone should not be used during adrenarche as clinical marker for metabolic control in CAH treatment.

Key Words: growth, adrenarche, classic CAH, final height prediction

Congenital adrenal hyperplasia (CAH) comprises a group of autosomal recessive disorders, in which an enzymatic deficiency leads to impaired glucocorticoid biosynthesis. The most common form of CAH is 21-hydroxylase deficiency due to variants in the *CYP21A2* gene, with a frequency of about 1 in 10 000 to 15 000 births (1). Because the glucocorticoid feedback system remains intact with CAH, the hypothalamus and anterior pituitary gland respond to low cortisol levels by releasing corticotropin (CRH) and adrenocorticotropin (ACTH) hormones, which increase steroid precursor synthesis upstream of the enzymatic defect. In 21-hydroxylase deficiency, accumulating precursors are converted to androgens that cause the typical clinical features of CAH. These include virilization of girls at birth, and adrenal insufficiency soon after birth in both sexes. Precocious pseudopuberty, growth acceleration, and advancement of bone age may occur in insufficiently treated infants, which may lead to reduced final height. Adverse outcomes are testicular adrenal rest tumors in boys, hirsutism, and menstrual cycle disturbances in girls, as well as fertility problems in both sexes (1).

Management of children with CAH remains a challenge. Because patients with a severe loss of 21-hydroxylase activity require lifelong replacement therapy with glucocorticoids and mineralocorticoids, finding the balance between hyperandrogenism and hypercortisolism is important. Undertreatment leads to insufficient hypothalamic-pituitary-adrenal axis suppression and excessive androgen production, which accelerates growth (2), while overtreatment with glucocorticoids directly inhibits growth (3). Throughout childhood and adolescence, close monitoring of biochemical markers and adjusting glucocorticoid dosage are necessary (4, 5).

Patients with CAH often do not reach their full growth potential (2, 6–8). Important factors that contribute to reduced final height are overtreatment with glucocorticoids, poor patient compliance, or direct effects of glucocorticoids

on growth and sex hormone secretion, or on bone, collagen, and muscle formation (3, 9, 10).

However, the exact contribution of these and unknown other factors remains unclear, but growth-inhibiting factors may have a different impact during different developmental periods in childhood (2). Puberty is a critical phase when changes in glucocorticoid pharmacokinetics complicate metabolic control and compromise height gain (11–13). An additional, earlier phase when growth may be influenced adversely is adrenarche, the onset of androgen production in the developing/maturing adrenal zona reticularis (zR) (14). During adrenarche, some CAH children with previously adequate metabolic control and skeletal maturation present with increased growth velocity and advancing bone age, and thus are assumed to require higher glucocorticoid doses.

Growth during adrenarche has been studied in healthy children extensively (14–19), but data on this topic in children with CAH are scarce. It remains unclear if compromised final height in CAH individuals originates in part from altered growth characteristics during adrenarche.

We therefore aimed to describe trends of skeletal maturation (bone age), height, growth velocity, and projected adult height in children with classical CAH throughout adrenarche and puberty. We also investigated potential risk factors for lower final height outcomes.

Methods

Study Population and Procedure

This is a retrospective multicenter study using patient data from digital and paper charts of 4 Swiss pediatric endocrinology centers. We received ethics approval through the Swiss DSD Cohort Study Registry, from the Ethics Committees of the Cantons of Bern, Zurich, Vaud, Geneva, and the Ethics Committees of Northwestern and Central Switzerland (EKNZ) and Eastern Switzerland (EKOS) (BASEC-ID 2016–01210).

We included children born from 1990 to 2012 with a neonatal diagnosis of classic CAH due to 21-hydroxylase deficiency and continuous follow-up care in the respective clinic between diagnosis and 9 years of age (Fig. 1). We excluded patients who received growth-promoting treatments (growth hormone [$n = 1$]), puberty blockage ($n = 1$), aromatase inhibitors ($n = 2$), or who did not provide informed consent. In Switzerland, nationwide screening for CAH was introduced in 1992. Five study patients were born between 1990 and 1992 but were still diagnosed in the first month of life.

We extracted clinical parameters from medical charts, including results from gene analyses, hand x-ray images, auxological measurements (weight and height), parental height, pubertal status (Tanner stage), medication, and laboratory measurements (17-hydroxyprogesterone [17-OHP], dehydroepiandrosterone sulfate [DHEAS], androstenedione).

We classified results from gene analyses according to international guidelines (1) into 4 groups (0, A, B, C) as described by Speiser et al (20).

Bone age was determined in yearly intervals using radiographs of the hand and the method of Greulich and Pyle (21). We reassessed all bone ages to avoid systematic measurement error between the 4 centers. We defined bone age retardation as the difference between bone age and chronological age (BA-CA). Standard deviation scores (SDS) for height, weight, body mass index (BMI) and growth velocity were derived using the LMS method (22) for Swiss references (23). Corrected final height SDS were calculated as the difference between final height SDS and target height SDS. We calculated estimated adult height based on bone age and height according to the Bayley-Pinneau method (24), as well as with the adapted values proposed for CAH patients by Bonfig and Schwarz (25). Parental target height was calculated as the mean height of both parents ± 6.5 cm for boys and girls, respectively. BMI was calculated as weight in kilograms divided by square height in meters. We considered patients with a growth velocity less than 1 cm/year and/or older than 18 years to have reached final height.

We used the Tanner method to define pubertal stages (26). We considered children with Tanner stage 1 as pre-pubertal, girls with thelarche B2 and G2 in boys as pubertal, and pubarche as P2 in both sexes. We grouped longitudinal data in 3 defined time periods: (a) *Before adrenarche*: aged <6 years; (b) *Adrenarche*: aged ≥ 6 years to puberty onset (corresponding to B2 in girls and G2 in boys); and (c) *Puberty*: after puberty onset.

We determined equivalent of hydrocortisone dosages in $\text{mg}/\text{m}^2/\text{d}$ for all visits to standardize assessment of glucocorticoid treatment. The glucocorticoid effect of

prednisolone is estimated to be 4 times as potent as hydrocortisone (5). Patients did not show signs of significant chronic over- or undertreatment during the observation period. We assigned patients as having received hydrocortisone dosages of $<15 \text{ mg}/\text{m}^2/\text{day}$ or $\geq 15 \text{ mg}/\text{m}^2/\text{day}$, and fludrocortisone dosages of $<50 \text{ }\mu\text{g}/\text{day}$ or $\geq 50 \text{ }\mu\text{g}/\text{day}$. We categorized patients into those with androstenedione levels $<11 \text{ nmol/L}$ or $\geq 11 \text{ nmol/L}$, and those with 17-OHP levels $<30 \text{ nmol/L}$ or $\geq 30 \text{ nmol/L}$.

Statistical Analyses

We compared age at entering a certain sexual development period (onset of Tanner stages) between patients with CAH and healthy European references using the Student t test (27).

We compared bone age and growth between girls and boys; between children aged <6 years and children during adrenarche; and between children during adrenarche and children during puberty using Wilcoxon rank-sum tests.

We categorized the cohort into 2 groups depending on their bone age progression: We categorized children whose yearly mean BA-CA was at least 0.1 year higher at age 6 to 9 years than <6 years as *accelerating* patients, and all other as *nonaccelerating* patients. We chose a cutoff at age 9 years to exclude pubertal growth spurt. We calculated means and 95% CIs by time period, and by bone age progression group. If 95% CIs did not include the mean of the respective other group, we assumed differences between accelerating and nonaccelerating patients.

We performed linear mixed effects models to identify factors associated with estimated final height SDS (Bayley and Pinneau (24)) separately for adrenarche and puberty. Estimated final height SDS data were normally distributed. We included patients and age as random effects and bone age progression, sex, Speiser classification (20), glucocorticoid dose, fludrocortisone dose, androstenedione, and 17-OHP as fixed effects. Because of the relatively small sample size, we ran univariable models only.

We used the statistical software Stata (Version 16, Stata Corporation, Austin, Texas) for data preparation, descriptive statistics, and calculation and visualizing of linear mixed model parameters. We created line charts and boxplots using the ggplot2 package for RStudio version Tiger Daylily.

Results

We included data from 41 patients with classic CAH in our study (Table 1). Of those, 15 were boys (37%) and 26 girls (63%). Most patients (31/41, 76%) had CYP21A2 genotyping to confirm diagnosis. Among those children with genetic analyses, 4/31 (13%) were in Speiser category

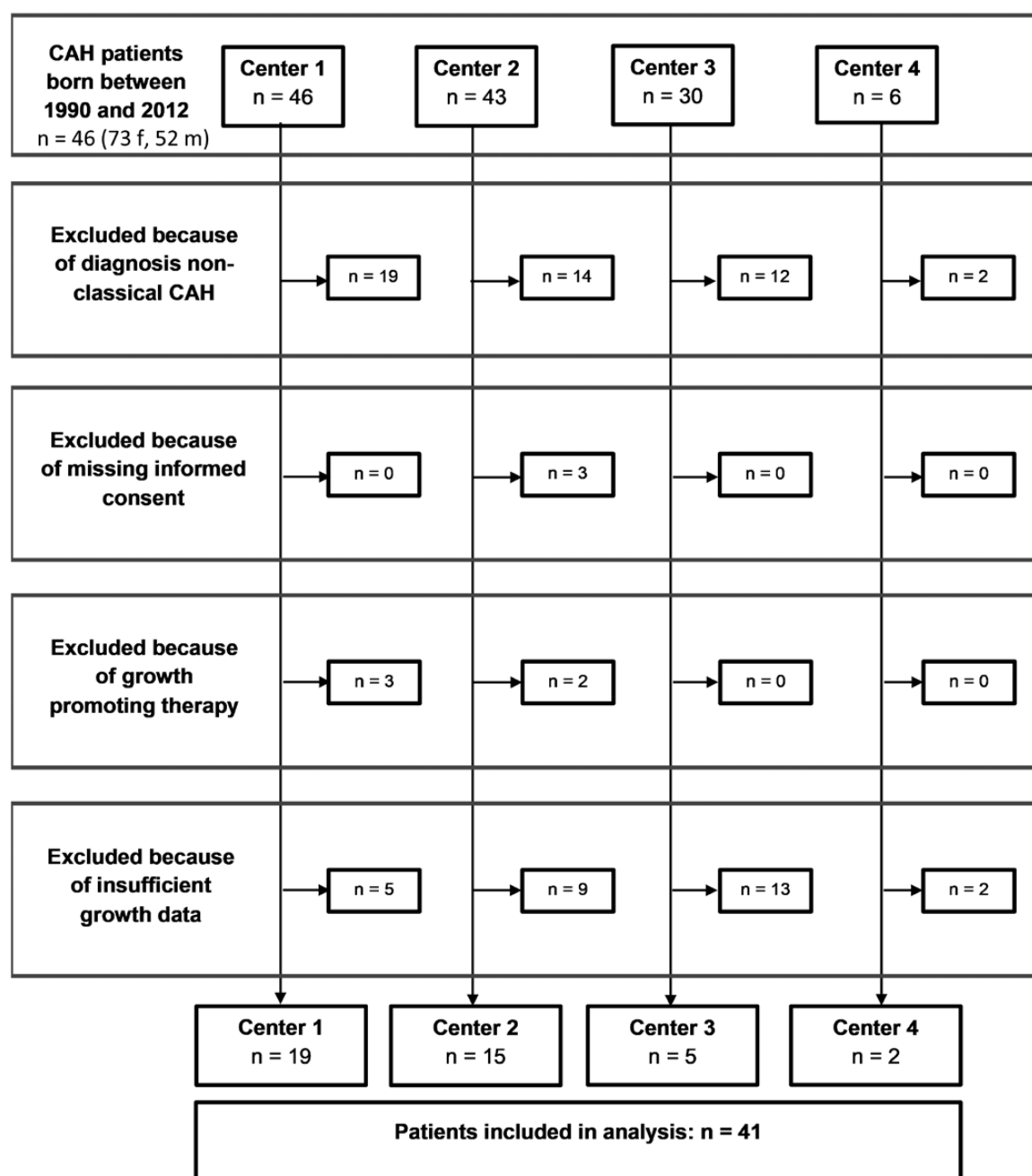


Figure 1. Recruitment scheme. Figure 1 depicts the patients recruited according to the inclusion criteria age, informed consent, and diagnosis with classical CAH in the 4 recruitment centers.

0, 12/31 (39%) in category A, 13/31 (42%) in category B, and 2/31 (6%) in category C. The most frequent mutations were deletions (16/31, 52%), intron 2-splice mutations (14/31, 45%), and I172N (13/31, 42%). At the time of the study, 37/41 CAH patients had developed pubarche, at a mean age of 10.5 years in girls and 11.7 years in boys. At the time of study, puberty had started in 35/41 of CAH patients. In girls, pubarche started at a mean age of 10.5 years and puberty at 10.3 years, slightly earlier than in European references (P2: 11.3 years; B2: 10.9 years) (27). Timing of

pubarche or adrenarche was similar between boys with CAH (P2: 11.7 years; B2: 12.1 years) and European references (P2: 11.9; G2: 11.8) (27).

Mean BMI was within normal range in both girls and boys (mean 0.3–1.3 SDS), but it increased from before adrenarche to adrenarche in both sexes ($P < 0.05$) (Fig. 2A). Patients received a mean hydrocortisone dose of 14.1 to 16.2 mg/m²/d, which did not vary between developmental periods ($P = 0.349$). Almost all (40/41) patients received fludrocortisone.

Table 1. Characteristics of patients with CAH

	All patients				Boys				Girls				P value ^a
	N = 41				N = 15				N = 26				
	n	%	Mean	SD	n	%	Mean	SD	n	%	Mean	SD	
Age at P2, years	35	85	10.9	1.6	11	73	11.7	0.9	24	92	10.5	1.6	0.013
Age at puberty, years	37	90	10.8	1.5	11	73	12.1	1.3	26	100	10.3	1.2	0.001
Mean BMI SDS ^b													
before adrenarche	41	100	0.4	0.9	15	100	0.5	1	26	100	0.3	0.9	0.885
adrenarche	41	100	1	0.8	15	100	1.3	0.9	26	100	1	0.7	0.646
puberty	36	88	0.9	0.9	11	73	1	1.2	25	96	0.9	0.7	0.74
Mean equivalent hydrocorticoid dosage (mg/m2/d) ^c													
before adrenarche	41	100	15.8	2.8	15	100	15	2.6	26	100	16.2	2.8	0.312
adrenarche	41	100	14.7	3.2	15	100	14.1	3	26	100	15.1	3.3	0.487
puberty	36	88	15.4	2.8	11	73	14.5	3.3	25	96	15.8	2.5	0.74
Mineralocorticoid dosage (µg/d)	41	100	63.2	34.5	15	100	58.5	27.3	26	100	65.7	37.4	0.591
Genotyping available	31	76			13	87			18	69			n.a.
Speiser classification ^c													
0	4	10			0	0			4	22			
A	12	29			4	31			8	44			
B	13	31			7	54			6	33			
C	2	5			2	15			0	0			
Mutations ^{c,d}													n.a.
Deletions/conversions ^e	16	52			6	46			10	56			
Intron 2 splice ^f	14	45			5	38			9	50			
I172N	13	42			6	46			7	39			
Other mutations:													
V281L	2	6			1	8			1	6			
Q318X	1	3			0	0			1	6			
962_963insA	1	3			0	0			1	6			
P30L	7	23			2	15			5	28			

Table presents genetic analysis, mutations, pubertal data, mean BMI SDS, as well as hydrocortisoid and fludrocortisone dosages of all patients combined, and separated for boys and girls.

Abbreviations: BMI, body mass index; n, number; n.a., not applicable; P2, Tanner pubic hair stage II; SDS, standard deviation score.

^aP values derived using the Wilcoxon rank-sum test, comparing boys and girls.

^bMean calculated for each period per individual patient.

^cMeans and percentages refer to the number of patients with available genotyping.

^dMultiple mutations per patient possible.

^eIncludes deletions and gene conversions of varying lengths, G110Δ8nt, and E6 cluster.

^fIntron2 Splice mutation 655C/A→G.

Growth Characteristics of Boys and Girls With CAH During Adrenarche and Puberty

To assess the growth characteristics of CAH patients, we analyzed longitudinal growth data in 3 time period groups: before adrenarche, adrenarche, and puberty (Table 2 and Fig. 2). Of the 41 children with CAH, 20/26 girls and 7/15 boys achieved final height with a mean of 160.1 and 176.4 cm respectively. Mean height SDS at age <6 years was in the low normal range and increased from <6 years to adrenarche ($P = 0.011$) (Fig. 2B). Mean growth velocity was higher in boys than in girls before adrenarche, but not afterward (Table 2). We observed that mean growth velocity in boys was higher before adrenarche than at puberty, while no difference between age periods was observed in girls (Fig. 2C). In both sexes, mean BA-CA was slightly delayed before adrenarche and increased with adrenarche (-0.5 years \pm 0.7 SD vs 0.1 years \pm 1.4 SD; $P = 0.014$, Fig. 2D, Table 2). We also observed a difference in mean BA-CA between girls and boys from before adrenarche to puberty (Fig. 2D).

When we compared estimated final height SDS between boys and girls, we found that boys had a higher estimated final height SDS according to Bayley and Pinneau (24) than girls during adrenarche (boys: 0.3 SDS \pm 1.0 SD vs girls: -0.7 SDS \pm 1.1 SD) and during puberty (boys: 0.3 SDS \pm 1.1 SD vs girls: -0.7 SDS \pm 0.9 SD) (Table 2). There was no difference between the time periods in either girls or boys for Bayley and Pinneau estimations (Fig. 2E). By contrast, estimated final height SDS increased from adrenarche to puberty in girls and boys when calculating with the Bonfig and Schwarz method (Fig. 2F).

Do CAH Children Who Advance Their Bone Age During Adrenarche Achieve a Lower Final Height?

When we divided CAH children by bone age progression during adrenarche, half of the children (20/41, 49%) had accelerating bone age, and in the other half (21/41, 51%) bone age progressed normally (Fig. 3A, B). Mean height SDS during adrenarche was higher in children with accelerating BA-CA than in those with nonaccelerating BA-CA (0.5 SDS [95% CI, 0.2; 0.9] vs -0.3 SDS [95% CI, -0.9 ; 0.2]) (Fig. 3C, D). During puberty, these differences disappeared (Fig. 3B and 3D). Growth velocity was higher before adrenarche in children with bone age progression during adrenarche and decreased thereafter (Fig. 3E).

Children with accelerating BA-CA during adrenarche had a lower estimated final height according to Bayley and Pinneau than those whose bone age was not progressing (-0.9 SDS [95% CI, -1.3 ; -0.5] vs 0.2 SDS [95% CI, -0.3 ; 0.8]), but this difference disappeared by the time they

reached puberty (Fig. 3G); the same was true when using the Bonfig and Schwarz method (Fig. 3H).

Factors Associated With Estimated Final Height

During adrenarche, accelerating bone age ($r -1.12$ [95% CI, -1.7 ; -0.5]), female sex ($r -0.98$ [95% CI, -1.6 ; -0.3]), and 17-OHP >30 nmol/L ($r -0.37$ [95% CI, -0.7 ; 0.0]) were associated with lower estimated final height, and fludrocortisone doses >50 μ g/day ($r 0.34$ [95% CI, 0.0; 0.6]) were associated with higher estimated final height (Fig. 4A). During puberty, female sex ($r -1.00$ [95% CI, -1.7 ; -0.3]) was associated with lower, and androstenedione >11 nmol/L ($r 0.25$ [95% CI, 0.1; 0.4]) with higher estimated final height (Fig. 4B). Children with a genetic diagnosis of Speiser category C ($r 1.67$ [95% CI, 0.9; 2.4]) seemed to be more likely to achieve a higher final height than children of other CAH diagnoses, but differences were not statistically significant, probably because some genetic subgroups contained only a few patients.

Discussion

Our study found that final height in patients with classic CAH is still compromised, although less than in earlier days. We therefore investigated whether height loss may be due to events occurring during the years of adrenarche. We identified 2 growth patterns during adrenarche, patients whose bone age accelerated in relation to their chronological age, and patients whose bone age progressed normally. Patients with accelerating BA-CA were taller during adrenarche and had lower estimated adult height than those with nonaccelerating BA-CA during adrenarche. During puberty, however, estimated final height was similar in both groups. Final height in both groups was similarly lower compared to the normal population and in relation to parental target height. Thus, we found that the transient acceleration of bone age during adrenarche cannot explain the reduced final height in CAH patients.

Similar to our results, a meta-analysis of 35 studies found that patients with classic CAH under corticosteroid treatment were shorter than healthy controls, and shorter than their parents (7). However, mean final height of our CAH patients was higher than in most previous studies (7), possibly because most patients reported in previous studies received higher average glucocorticoid doses of 15 to 20 mg/m²/d. Our patients received 14.7 or 15.4 mg/m²/d during adrenarche and puberty, respectively, as recommended by Bonfig et al (4, 28). In addition, neonatal screening allowed for rapid diagnosis and treatment in our patients, contrary to some patients included in previous studies. Similar to our study, the meta-analysis also found that mineralocorticoid treatment increased final height

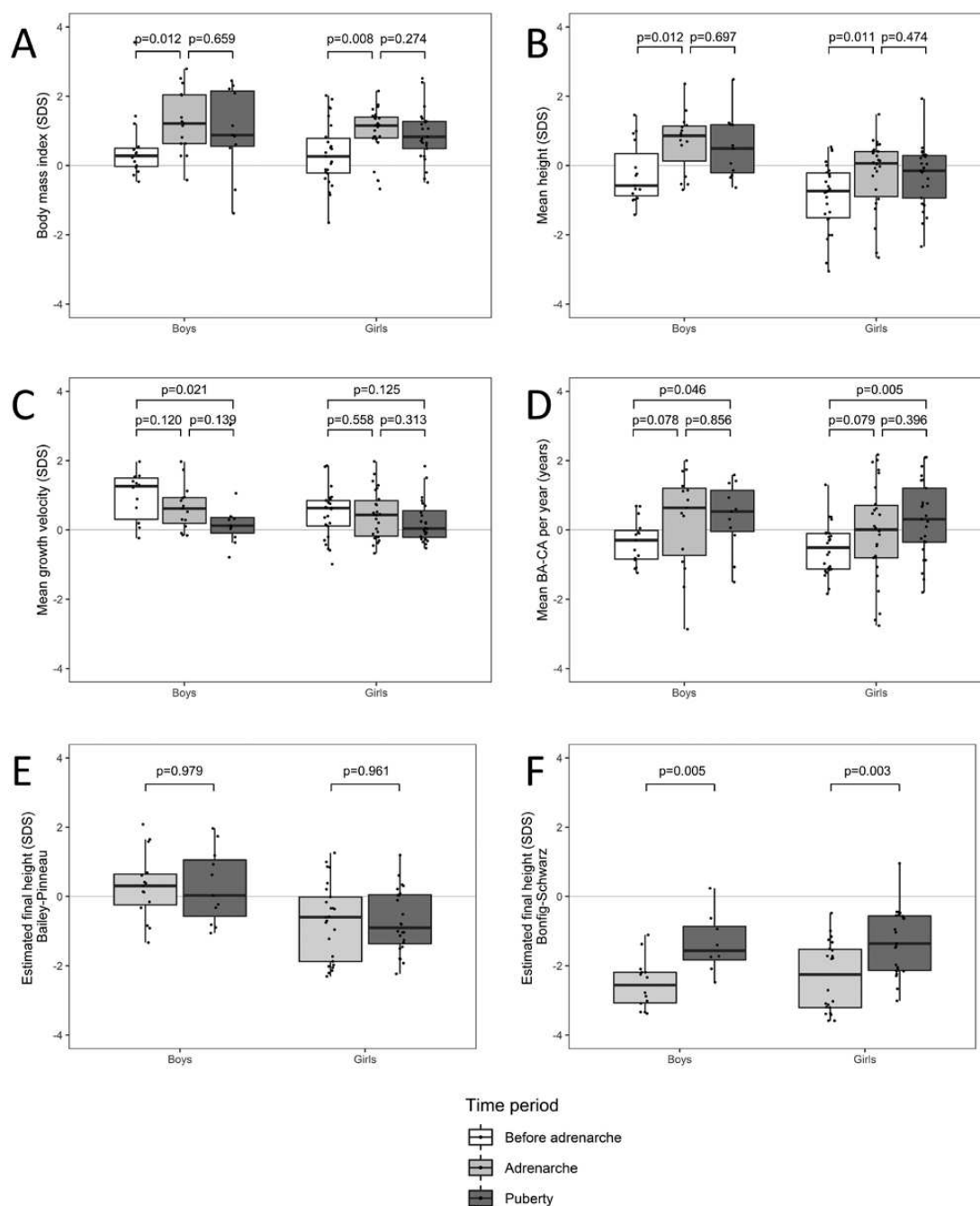


Figure 2. Growth characteristics of boys and girls with classic CAH before, during and after adrenarche. Shown are growth data of boys and girls, depicted in box plots and divided into 3 age groups: before adrenarche, adrenarche, and puberty. From top left to bottom right, parameters depicted as box plots are A, mean BMI SDS; B, mean height SDS; C, mean growth velocity SDS; D, mean bone age—chronological age (BA-CA); E, mean estimated height SDS according to Bailey and Pinneau (24); and F, mean estimated height SDS according to Bonfig and Schwarz (25).

outcomes (7). This positive effect might reflect early diagnosis and treatment in salt-wasting CAH children compared with later manifesting and treated non-salt-wasting CAH. All but 1 patient in our study received mineralocorticoids. Differences in patient compliance or in health care systems may in addition explain some differences in growth outcomes between our and previous studies.

In our CAH patients, pubertal growth spurt was similar to healthy children (29). This is in contrast to the study by Bonfig et al (28), where pubertal growth was lower in CAH than in healthy children. This suggests that pubertal growth did not compromise final height in our patients.

Female gender was a risk factor for low final height prediction in adrenarche and puberty. But studies on

Table 2. Auxological data of patients

	n	All patients N = 41		n	Boys N = 15		n	Girls N = 26		P value ^c
		Mean	SD		Mean	SD		Mean	SD	
Final height, cm				7	176.4	7.1	20	160.1	4.8	0.001
Final height SDS	27	-0.4	0.8	7	-0.2	1.0	20	-0.5	0.7	0.267
Accelerating patients	11	-0.4	0.7	3	0.0	1.0	8	-0.6	0.6	0.414
Nonaccelerating patients	16	-0.3	0.9	4	-0.1	1.1	12	-0.4	0.8	0.626
Parental target height, cm				15	179.2	4.2	26	163.7	4.5	0.001
Parental target height SDS	41	0.2	0.6	15	0.4	0.6	26	0.1	0.7	0.194
Corrected final height SDS ^a	27	-0.6	1.0	7	-0.2	1.2	20	-0.8	0.9	0.184
Mean height SDS ^b										
Before adrenarche	41	-0.7	1.0	15	-0.2	0.9	26	-0.9	1.0	0.110
Adrenarche	41	0.1	1.1	15	0.7	0.9	26	-0.2	1.0	0.004
Puberty	36	0.0	1.0	11	0.5	0.9	25	-0.3	0.9	0.031
Growth from G2/B2 to final height (cm)	27	20.7	6.4	7	22.5	8.3	20	20.1	5.8	0.543
Mean growth velocity SDS ^b										
Before adrenarche	41	0.6	1.2	15	1.2	1.0	26	0.3	1.0	0.006
Adrenarche	41	0.5	0.7	15	0.6	0.8	26	0.4	0.7	0.427
Puberty	36	0.2	0.7	11	0.3	0.7	25	0.2	0.7	0.693
Bone age – chronological age ^b										
Before adrenarche	41	-0.5	0.7	15	-0.3	0.6	26	-0.6	0.7	0.256
Adrenarche	41	0.1	1.4	15	0.3	1.4	26	-0.1	1.4	0.417
Puberty	36	0.3	1.1	11	0.4	1.0	25	0.3	1.1	0.878
Mean estimated final height SDS according to Bayley and Pinneau ^b										
Before adrenarche	41	-0.3	0.9	15	-0.1	0.9	26	-0.4	0.8	0.48
Adrenarche	40	-0.3	1.2	15	0.3	1.0	25	-0.7	1.1	0.011
Puberty	35	-0.4	1.1	11	0.3	1.1	24	-0.7	0.9	0.021
Mean estimated final height SDS according to Bonfig and Schwarz ^b										
Adrenarche	37	-1.3	1.1	15	0.3	1.0	22	-2.3	1.0	0.001
Puberty	34	-0.8	1.2	11	0.3	1.1	23	-1.3	1.0	0.007

Table presents number (n), mean, and SD of auxological data of all patients combined, and divided for boys and girls.

^aFinal height SDS – target height SDS.

^bMean calculated for each period per individual patient.

^cP values derived using the Wilcoxon rank-sum test, comparing boys and girls.

differences in final height between sexes are contradictory (7). Some studies reported decreased pubertal growth in boys (2, 30), potentially because CAH in boys was diagnosed at a later age than in girls before neonatal screening became standard of care (4, 30–32).

We saw a trend that final height estimation decreased with the severity of the genetic mutation in *CYP21A2*, which correlates well with 21-hydroxylase enzyme activity, but results were not statistically significant due to low sample size.

Final height estimations were better with low 17-OHP in adrenarche, and with high androstenedione levels in puberty. While the first finding informs about good metabolic control, the latter correlates with gonadal activation of sex hormone production stimulating growth.

Bone age is usually used as a clinical marker for metabolic control in CAH, with accelerated bone age indicating

glucocorticoid undertreatment (1). To achieve adequate final height in growing CAH patients with advanced bone age, international guidelines recommend increasing glucocorticoid dosage or considering height-promoting therapies, such as growth hormone treatment or aromatase inhibitors for CAH patients with a height of <–2.25 SDS (33). However, our CAH patients with and without significant bone age advancement, and thus differing final height prediction during adrenarche, had similar final height outcomes, when reassessed during puberty or reaching final height. This finding was unexpected, and we still search for an explanation. Looking at the old literature from Tanner et al, a similar growth pattern has been described for early and late bloomers, in whom bone age differed during puberty and hinted a higher final height outcome for late bloomers, but actual final height was same in both (26, 34). For our CAH patients, final height predictions using

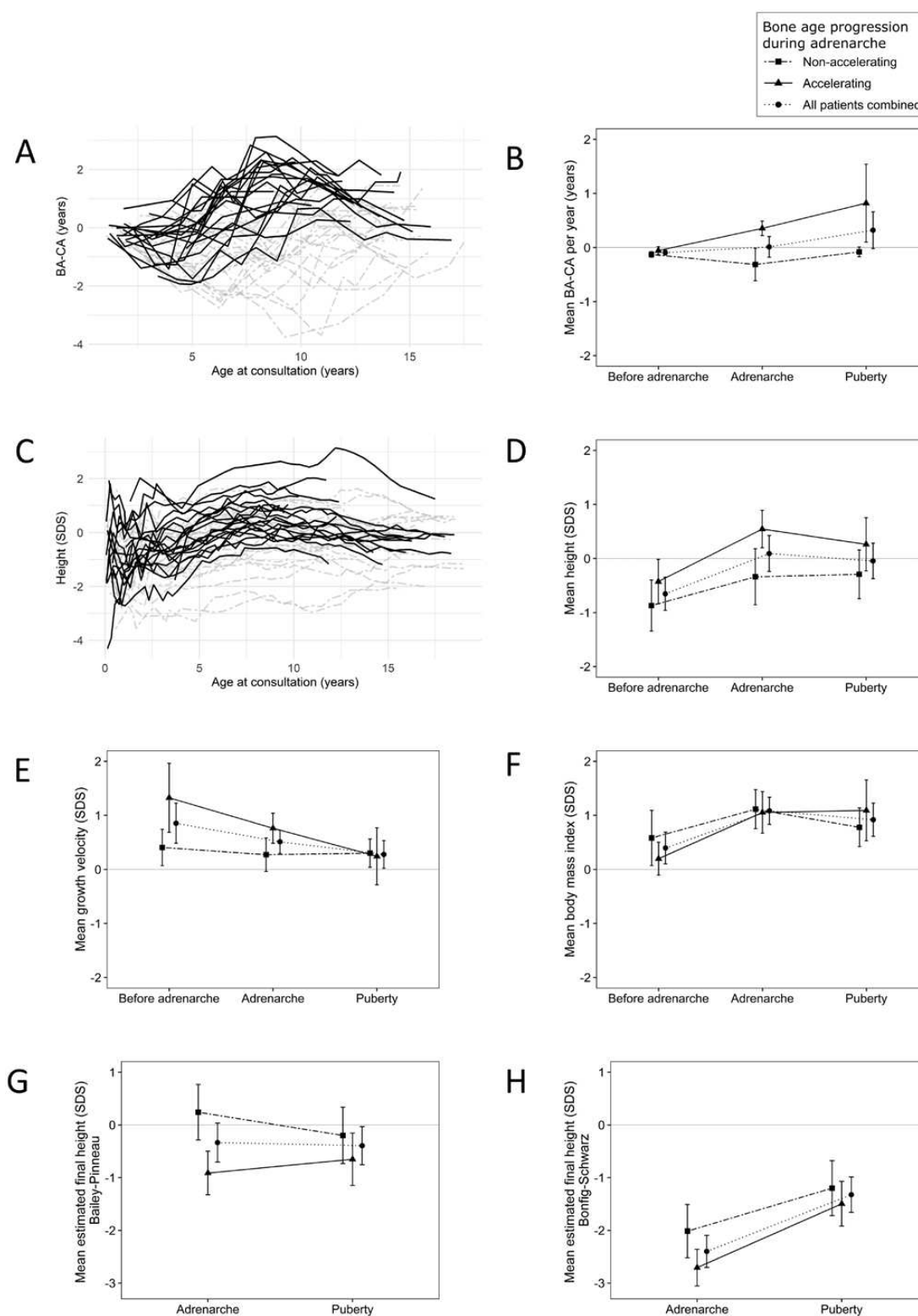


Figure 3. Growth data of CAH children showing accelerating or nonaccelerating bone age. Shown are dichotomized growth data of accelerating and nonaccelerating CAH children, and of all patients combined, depicted as line graphs and divided into 3 age groups: before adrenarche, adrenarche, and puberty. From top left to bottom right, parameters depicted are A, individual bone age – chronological age (BA-CA) of accelerating individuals (black) vs nonaccelerating (light gray) over time; B, mean BA-CA; C, individual height of accelerating individuals (black) vs nonaccelerating (light gray) over time; D, mean height SDS; E, mean growth velocity SDS; F, mean BMI SDS; G, mean estimated height SDS according to Bailey and Pinneau (24); and H, mean estimated height SDS according to Bonfig and Schwarz (25).

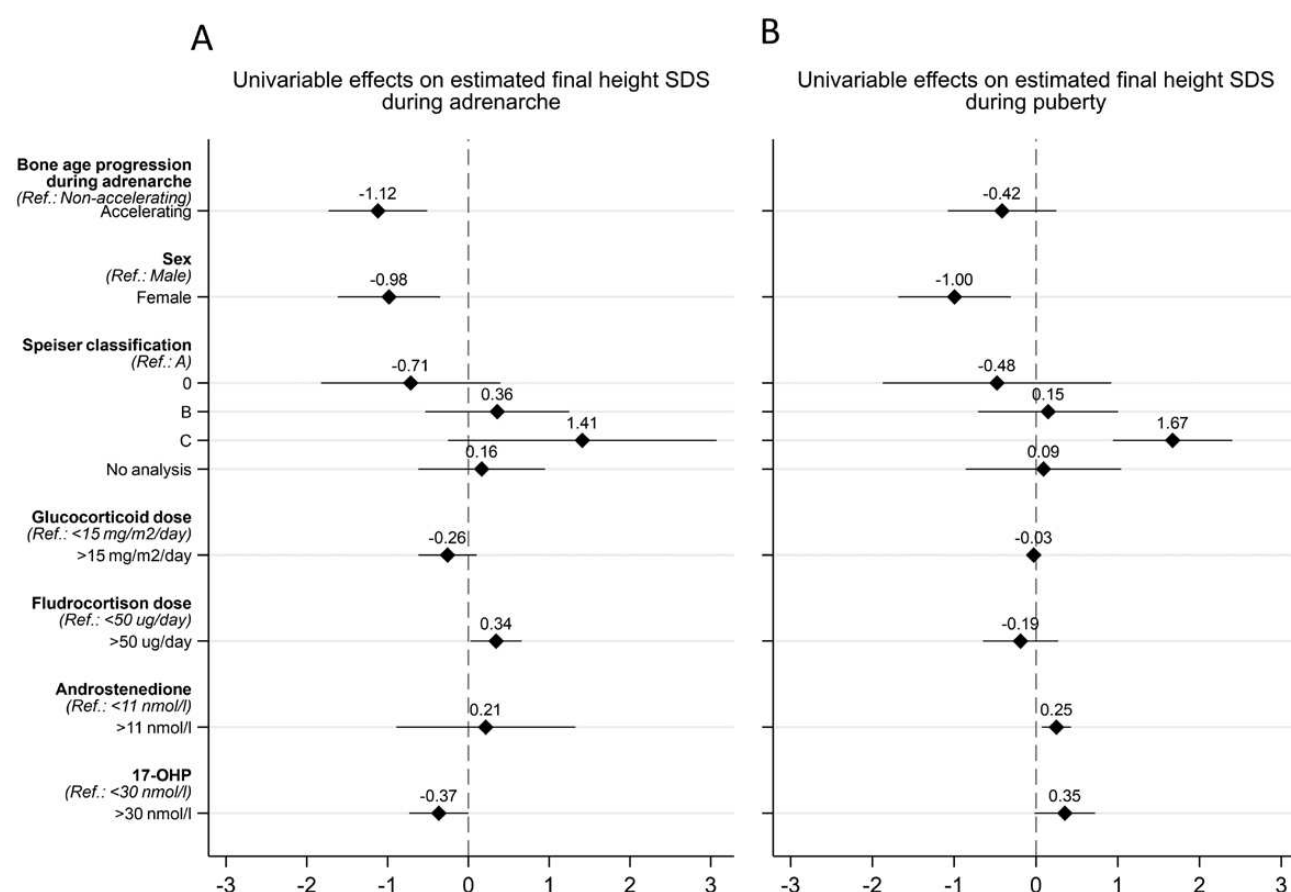


Figure 4. Coefficient plots showing factors associated with height outcome in CAH. This figure shows linear mixed effects models to identify factors associated with estimated final height SDS according to Bayley and Pinneau (24), separately for A, adrenarche and B, puberty.

the Bayley-Pinneau method (24) were most accurate to real final height, while the Bonfig and Schwarz method (25) underestimated final height at both time points adrenarche and puberty. Thus, bone age and height predictions should be treated with caution, and additional diagnostic, such as biochemical parameters, might help to monitor metabolic control in CAH children. Our data indicate that bone age alone should not be used during adrenarche as clinical marker for metabolic control in CAH treatment.

Adrenal androgens are produced in the zona reticularis (zR) of the adult adrenal cortex after adrenarche. The fetal adrenal involutes in the first weeks after birth and gives rise to an adult adrenal cortex, which consists initially only of the mineralocorticoid producing zona glomerulosa and glucocorticoid producing zona fasciculata (35-37). The zR forms continuously during infancy and becomes functionally active with adrenarche after the age of 6 to 9 years (38). Androgen precursors dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS), androstenedione, and 11-hydroxy-androstenedione are then produced in the zR and released into circulation and the intermediate metabolism where they may be converted to active 11-oxygenated androgens, such as 11-keto-testosterone (39). So far,

adrenarche has been defined by serum DHEAS $\geq 1 \mu\text{mol/L}$ biochemically (14), and by first appearance of pubic and axillary hair and adult-type body odor clinically (14, 40). However, clinical signs (pubarche) and biochemical markers (DHEAS) of adrenarche can be dissociated, as shown in girls with Turner syndrome (41), or misleading, as shown in CAH (42). Several studies have shown that pubarche appears earlier in CAH children than in healthy controls (28, 43, 44). Other studies have found low serum DHEAS levels in well-controlled children with classic CAH when compared to healthy controls regardless of their age (42, 45, 46). Therefore, authors concluded that it is difficult to define adrenarche in patients with CAH using the current clinical or biochemical definition, and that CAH patients might not have an adrenarche at all (42, 45, 47). Defining adrenarche biochemically was impossible in our patients because they had low DHEA/S (androgen) levels throughout childhood and adolescence, in line with other studies (42, 44, 47, 48). Glucocorticoid therapy of CAH suppresses adrenal androgens, influencing the physiological timing of pubic hair appearance (pubarche). Therefore, we defined the time period of adrenarche as between age of 6 years to the onset of puberty.

Strength and Limitations

A limitation we share with most other studies on growth in CAH patients is the retrospective design. This may explain the observed difference in sex ratio from the expected 1:1 sex ratio in CAH. Boys with CAH may be more likely than girls to drop out of follow-up care; thus, the participating clinics may have missed a few during patient identification. In Switzerland, children with CAH see their treating pediatric endocrinologist in at least 6-monthly intervals. This may have led to underestimation of the age at puberty. We therefore used a defined age range from 6 to 9 years to determine bone age progression during adrenarche to exclude pubertal growth spurt. The relatively low sample size led to wide confidence intervals for subgroups of CAH patients. Thus, we may have missed detecting differences in height outcomes between patients with accelerating and nonaccelerating bone age, or differences between genetic subgroups on estimated final height. But the slightly smaller adult height in our CAH children compared with their peers has no clinical significance. Studies with a larger number of patients are important to confirm our findings and may be feasible through collaborative efforts using an international registry such as the I-CAH (<https://home.i-cah.org/>). Only two-thirds of our CAH patients had reached final height during the time of the study. In a follow-up study, when all patients have achieved final height, we will be able to draw more robust conclusions whether, and to which extent, bone age progression influences final height.

We used 2 established methods to describe estimated final height in CAH. Bayley and Pinneau developed a method to predict final height from bone age progression in healthy children (24). To avoid overestimation of final height in CAH children, we calculated all final height projections using the Bayley and Pinneau method assuming that bone age was adequate for chronological age. We also used the method by Bonfig and Schwarz, which they adapted specifically for children with classic CAH (25). In our setting, predictions using average values of Bayley and Pinneau were closer to final height than when using Bonfig and Schwarz predictions.

Conclusion

CAH patients under recommended near-physiologic glucocorticoid treatment achieve a final height that is close to normal. Although a growth acceleration and bone age progression can be observed in almost 50% of children during the years of adrenarche, this does not result in a more compromised (predicted) final height compared with CAH children who do not have bone age progression during adrenarche. Thus, bone age may not be the best

marker of metabolic control in CAH patients during the period of adrenarche, and additional growth-promoting treatments in otherwise well-controlled CAH patients seem unnecessary.

Acknowledgments

We thank all patients and families for contributing to this study. We also thank the members of the Swiss DSD Cohort Study for support: Melanie Hess, Basel; Anna Lauber-Biason, Fribourg; Valerie Schwitzgebel and Mirjam Dirlewanger, Geneva; Michael Hauschild and Kanetee Busiah, Lausanne; Dagmar l'Allemand and Katrin Heldt, St.Gallen; Paolo Tonella, Luzern; Franziska Phan-Hug, Morges and Sion; Ursina Probst, Winterthur; Michael Steigert, Chur; Jürg Streuli, Zürich; Udo Meinhardt, Stefanie Wildi-Runge, Annik Hauri-Hohl and Silvia Schmid, Dübendorf.

Financial Support: This study was supported by a grant of the "Batzebar" Foundation of the University Children's Hospital Bern, of Oak Foundation, Geneva, Boveri Foundation, Zürich, as well as by Novo Nordisk Switzerland.

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Disclosures: All authors declare no competing interest, except C.E.F. who is supported by independent research grants and performs clinical studies with Novo Nordisk Switzerland.

Data Availability: Data generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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